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Effect of Acids on Certain Carbocyclic Antiseptics.

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During the course of recent experimental studies on the pathology and treatment of burns directed toward reducing the incidence of infection associated with the Davidson tannic acid treatment, the addition of various antiseptics was considered. Aldrich¹ had pointed out the low antiseptic value of tannic acid alone and noted the frequency of infection beneath the heavy eschar. In view of his findings, Aldrich substituted crystal violet for tannic acid in the treatment of burns. Experimentally, burns treated with crystal violet, either alone or in combination with tannic acid, allowed the development of *B. pyocyaneus* and the colon group. Obviously, the proper antiseptic must be compatible with tannic acid, must have high bactericidal value against both cocci and bacilli, and low toxicity for tissue cells both locally and generally.

The carbocyclic group of compounds seemed to give the most promise of satisfying these criteria, and amyl tricresol (Upjohn and Company) was the first one tried. This material used in 1-1000 concentration with 5% or 10% tannic acid reduced the incidence of infection in experimental burns satisfactorily and at the same time did not interfere with the healing of the wounds.

Bactericidal tests (Food and Drug Administration Method) showed amyl tricresol effective in dilutions of 1-2000 against *E. typhi* and in dilutions of 1-4000 against *S. aureus* in 10 minutes. In combination with 5% tannic acid it became effective in dilution of 1-12,000 against *E. typhi* and 1-8000 against *S. aureus* in 10 minutes. Thus the effectiveness of amyl tricresol was increased 6 times against *E. typhi* and 2 times against *S. aureus* through combination with tannic acid.

Other organic acids have been found to have a comparable synergistic effect, *i. e.*, citric, tartaric, salicylic, benzoic, gallic, and lactic, when the pH of the solutions is maintained at a point between 2 and 3. Effectiveness is increased with greater concentrations of acid and decreased with dilution or buffering of the solutions.

Of the inorganic acids, only boric and hydrochloric were tested, and of these hydrochloric alone showed appreciable effectiveness.

¹ Aldrich, R. H., *New Eng. Med. J.*, 1933, **208**, 299.

Used in concentration of 0.36% by weight, this acid, combined with amyl tricresol, showed the effective dilution to be 1-28,000 against *E. typhi* and 1-24,000 against *S. aureus* in 10 minutes, increases of 17 and 6 times respectively over that of the tricresol. The striking increase in bactericidal activity due to the combination of tricresol with tannic and hydrochloric acids demonstrated by these observations placed these combinations in the group of most efficient antiseptics and led us to test other combinations as shown in Table I.

TABLE I.

Substance (F. & D. A. Method)	Dilution effective in 10 minutes <i>E. typhi</i> 20° C. <i>S. aureus</i> 37° C.	
Amyl tricresol 1-2000 (U)	2000	4000
Glycerine 50%, alcohol 25%		
Amyl tricresol 1-2000 (U)	12000	8000
Glycerine 50%, alcohol 25%, tannic acid 5%		
Amyl tricresol 1-2000 (U)	28000	24000
Glycerine 50%, alcohol 25%, HCl 0.36%		
Dihydroxy-n-hexyl benzene (S)	4000	4000
" " , tannic 5%	16000	4000
" " , HCl 0.36 %	28000	20000
Di-hydroxy-di sec. hexyl-benzene (P)	2000	52000
Glycerine 50%, alcohol 25%		
Di-hydroxy-di sec. hexyl-benzene (P)	4000	52000
Tannic acid 5%, glycerine 50%, alcohol 25%		
Di-hydroxy-di sec. hexyl-benzene (P)	20000	76000
HCl 0.36%, glycerine 50%, alcohol 25%		
Di-hydroxy-hexyl-ethyl benzene 1-1000 (H)	1000	24000
Di-hydroxy-hexyl-ethyl benzene 1-2000 (H)	32000	60000
HCl 0.36%		
Di-hydroxy-hexyl-ethyl benzene 1-2000 (H)	20000	36000
Tannic 5%		
Di-hydroxy-hexyl-chloro-benzene 1-200 (H)	2000	28000
Glycerine 50%, alcohol 25%		
Di-hydroxy-hexyl-chlorobenzene 1-2000 (H)	24000	36000
Glycerine 5%, alcohol 25%, tannic 5%		
Di-hydroxy-hexyl-chloro-benzene 1-2000 (H)	48000	68000
Glycerine 5%, alcohol 25%, HCl 0.36%		
Chloro-thymol 1-2000	2000	2000
Glycerine 50%, alcohol 25%		
Chloro-thymol 1-2000	16000	12000
Tannic acid 5%, glycerine 50%, alcohol 25%		
Chloro-thymol 1-2000	32000	24000
HCl 0.36%, glycerine 50%, alcohol 25%		
Di-hydroxy-di-octyl-benzene 1-1000 (P)	20000	28000
Glycerine 20%, HCl 0.36%		
Di-hydroxy-di-heptyl-benzene 1-1000 (P)	24000	28000
Glycerine 20%, HCl 0.36%		
Di-hydroxy-di-hexyl-chloro-benzene 1-2000 (H)	35000	70000
HCl 0.36%, alcohol 90%		
Hexyl-p-chloro-m cresol 1-2000 (H)	36000	200000
Glycerine 20%, HCl 0.36%		
Hexyl-p-chloro-m cresol 1-2000 (H)	4000	124000
Tannic acid 5%, glycerine 20%		

U—Upjohn and Company. S—Sharp and Dohme. P—Parke, Davis Company.
H—Henry Ford Hospital.

It is apparent from the data presented that many of carbocyclic compounds which have been considered relatively ineffective antiseptics or which have been effective against one group of organisms and ineffective against other groups are greatly enhanced in value in the first instance and become more uniformly effective against all groups of bacteria in the second instance by the combination with certain acids. The pH needs to be decreased only to 2 or 3 to get a marked increase in the effectiveness, and such relatively low pH is preferred because this adds little to the tissue toxicity. However, higher concentrations of acid will further increase the effectiveness and lower concentrations will decrease the effectiveness as will buffering the solutions. Aside from the pH there is a difference in acids as far as the effectiveness of the combination is concerned. For example, the pH of 5% tannic acid and 0.36% hydrochloric acid are comparable, but the combinations with the latter are invariably much more effective.

Although phenol coefficients are not calculated in this series, approximate phenol coefficients may be estimated by dividing the figure listed by 100. Further, it should be kept in mind that phenol coefficients calculated on the F.D.A. method range from 25 to 40% below those calculated on the Hygienic Laboratory method, since 0.5 cc. of culture is used in the former rather than 0.1 cc. as in the latter, and the specified strains of *E. typhi* and *S. aureus* are more resistant.

In addition to the surprisingly high effectiveness against bacteria of the combinations listed, experimental and clinical application to burned areas, granulating surfaces and wounds generally demonstrates that as a group they have low toxicity locally and no systemic evidence of toxicity has been found. Intravenous administration of the various dihydroxy benzenes (resorcinols) with hydrochloric acid 0.36% by weight is well borne by animals, and the effects on various bacteria in the circulating blood and upon the various organs will be reported in a later communication.